REMARKS

Applicant requests reconsideration of the application in view of the foregoing amendments and the discussion that follows. The status of the claims as of this amendment is as follows: Claims 1-8, 10-24 and 37-46 are pending. Claims 7, 8, and 10-24 were previously withdrawn and are canceled herein and Claims 9 and 25-36 were previously canceled. Applicant reserves the right to file divisional applications to the separately patentable subject matter thereof. Claims 1, 3, 44 and 46 have been amended herein.

The Amendments

Claim 1 was amended to refer to substrate as the entity that is bound to the support and to detectable product as the entity that is released from the substrate as a result of the cleavage. Support therefor is in the Specification, for example, page 4, lines 20-26.

Claim 3 was amended to recite that the third specific binding pair member is avidin bound to a member of a signal producing system or anti-digoxigenin antibodies bound to a member of a signal producing system or both. Support therefor is in the Specification, for example, Example 5.

Claim 44 was amended in a manner similar to that for Claim 1.

Claim 46 was amended in a manner similar to that for Claim 3.

Drawings

Applicant submitted replacement sheets for Figures 9, 10A and 10B in an Amendment under 37 C.F.R. 1.116 mailed on May 24, 2005, to obviate an objection to the drawings in the Final Rejection. Applicant assumes that the replacement sheets were accepted. If Applicant's assumption is incorrect, Applicant respectfully requests the opportunity to re-submit the replacement sheets.

Rejection under 35 U.S.C. 112

Claims 1-6 and 37-46 were rejected under the second paragraph of the above code section as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, the Office Action alleges that for Claims 1 and 44 the term "substrate" is indefinite. Applicant believes that the amendments to the rejected claims obviate this ground of rejection.

Claim 1 was also rejected for the recitation "or indirectly" as indefinite because it is not clear what type of spatial relationship is created by "indirectly" binding or which entities are included in the binding interaction. Furthermore, continues the Office Action, a person of ordinary skill in the art cannot ascertain the standard or degree of indirectness required by "indirectly."

Applicant respectfully traverses this ground of rejection. The Specification, page 54, lines 6-10, recites as follows: The term "capable of binding directly or indirectly" means that the designated entity can bind specifically to the analyte or assay component (directly) or can bind specifically to a specific binding pair member or to a complex of two or more sbp members which is capable of binding the other analyte or assay component (indirectly). As can be seen, indirect binding is defined as binding specifically to a specific binding pair member or to a complex of two or more sbp members capable of binding the analyte or assay component. This binding is indirect because the binding is not directly to the analyte or assay component but rather to another entity that binds to the analyte or assay component such as a specific binding pair member that binds to the analyte or assay component or to a complex of two or more sbp members that bind to the analyte or assay component.

As the language applies to Claim 1, therefore, a third specific binding pair member binding indirectly to the released detectable product would involve a situation where the third specific binding pair (sbp) member binds to a specific binding pair member that binds to the released detectable product or that binds to a complex of two or more sbp members that bind to the released detectable product. Accordingly, one skilled in the art would have an understanding of the meaning of the phrase as used in Claim 1.

Applicant submits that the amendments to Claim 3 obviate the rejection of Claim 3 under the second paragraph of the above code section regarding the relationship between the third specific binding pair member and avidin or anti-digoxigenin antibodies.

The Office Action contends that it is not clear what the purpose of using both avidin and anti-digoxigenin antibodies to detect a single product. Such a situation would provide,

e.g., for enhanced specificity and sensitivity because there would be two entities binding to a single product. In Claim 3 the substrate comprises digoxigenin linked biotin. If the linking group is of a length sufficient to permit both avidin and anti-digoxigenin antibodies to bind to the cleaved digoxigenin linked biotin, enhanced detection may be realized.

Applicant respectfully traverses the rejection of Claim 3 as indefinite for the recitation of signal producing system. The Office Action asserts that it is not clear what entities consist of, or comprise, a "signal producing system: or whether or how such entities are bound to avidin or anti-digoxigenin antibodies or how the entities function in the step of detection. The Office Action asserts that it is not clear whether or how all of the reagents required to produce a measurable signal are bound to avidin or anti-digoxigenin antibodies. In addition, the Office Action contends that it is not clear why more than one signal producing system is needed or why it is necessary to duplicate the signal producing system of Claim 1.

First, Claim 3 recites that the avidin or anti-digoxigenin antibody is bound to a "member" of a signal producing system, not to all members of the signal producing system. Second, Claim 1 does not mention a signal producing system and, therefore, the signal producing system recited in Claim 3 does not duplicate any system of Claim 1.

The signal producing system is discussed in the Specification, page 15, line 27, to page 17, line 2. The signal producing system may have one or more components or members at least one of which is a label or reporter group or reporter molecule. Claim 3 merely recites that avidin or anti-digoxigenin antibody is bound to one member of the signal producing system. There may be other members of the signal producing system that might be required such as, e.g., where an enzyme label is employed and a co-enzyme or enzyme substrate is also used. In such a case, sensitivity may be enhanced by having, e.g., avidin bound to an enzyme and anti-digoxigenin bound to an enzyme substrate.

Applicant's comments above apply equally to the rejection of Claim 46 under the second paragraph of the above code section.

Rejection under 35 U.S.C. 102

Claims 1, 2 and 4-6 were rejected under paragraph (e) of the above code section as being anticipated by Singh, *et al.* (U.S. Patent No. 6,770,439) (Singh).

Singh does not disclose or suggest the method of Claim 1. Among others, there is no disclosure or suggestion in Singh of a method as recited wherein the step of detecting the released detectable product comprises the steps of (a) separating the released detectable product from the substrate associated with the support; (b) adding to the separated released detectable product, a third specific binding pair member capable of binding directly or indirectly to the released detectable product; (c) allowing the third specific binding pair member to bind to the released detectable product; and (d) detecting the bound third specific binding pair member.

The Office Action argues that Singh teaches a method for amplifying a signal from a binding assay wherein the step of detecting the released detectable product comprises the steps of: separating the released detectable product from the substrate associated with the support, adding to the separated released detectable product a third specific binding pair member capable of binding directly to the released detectable product, allowing the third specific binding pair member to bind, and detecting the bound third specific binding pair member. In support of this contention, the Office Action refers to col. 29, lines 6-8, and Fig. 3B of the reference).

At col. 29, lines 6-8, and Fig. 3B, the patentee discusses the use of a capture ligand. As used by Singh, the term "capture ligand" refers to a group that is typically included within the target binding moiety or portion of an e-tag probe and is capable of binding specifically to a "capture agent" or receptor. The interaction between such a capture ligand and the corresponding capture agent may be used to separate uncleaved e-tag probes from released e-tag reporters (col. 17, lines 12-18). This disclosure has no informative value with regard to the presently claimed method. In particular, Claim 1 recites "a third specific binding pair member capable of binding directly or indirectly to the released detectable product" and "detecting the bound third specific binding pair member." In Singh the capture agent binds to the capture ligand of the uncleaved e-tag probes. See also Fig. 3B. Furthermore, there is no disclosure or suggestion in Singh of detecting the bound third specific binding pair member.

The Office Action responds to the above argument by referring to col. 40, lines 25-41 of Singh in support of the proposition that the "capture ligand" or "capture agent" of Singh is not limited in use for separating uncleaved e-tag probes from released e-tag

reporters. The cited passage states that "After washing, the support may be combined with a liquid into which the e-tag reporters are to be released and/or the functionality of the e-tags is reacted with the detectable label, followed by or preceded by release." The Office Action contends that Singh, therefore, teaches that e-tags can be reacted with a detectable label before or after the e-tag reporters are released or cleaved.

This argument is not persuasive. Simply because Singh states that the e-tags can be reacted with a detectable label before or after the release of e-tag reporters does not change what Singh teaches as the function of his capture ligand. Singh states at col. 17, lines 12-18 that "As used herein, the term 'capture ligand', refers to a group that is typically included within the target binding moiety or portion of an e-tag probe and is capable of binding specifically to a "capture agent" or receptor." This is the definition given the phrase by the patentee. The argument in the Office Action cannot change this fact.

With regard to the rejection of Claims 2 and 4-6, respectively, at the very least these claims are patentable over the reference because of their respective dependence from Claim 1, which is patentable over the reference as discussed above.

Rejection under 35 U.S.C. 103

Claims 3 and 37-43 were rejected under paragraph (a) of the above code section as being unpatentable over Singh in view of Oh and Steinberg (U.S. Patent No. 5,851,77) (Oh). The Office Action (page 6, penultimate paragraph) contends that Singh teaches a substrate comprising digoxigenin linked biotin and refers to col. 29, lines 6-8, and Figs. 3A and 3B in support of this proposition. However, in the last paragraph on page 6, the Office Action states that Singh does not teach a substrate comprising digoxigenin linked biotin. Applicant requests clarification for what appears to be a contradiction in these comments.

In any event the cited passages of Singh do not teach digoxigenin linked biotin. At col. 29, lines 5-15, the patentee, in discussing capture ligands, states that other reagents that are useful include a ligand-modified nucleotide and its receptor. Ligands and receptors include biotin and strept/avidin, ligand and antiligand, e.g. digoxin or derivative thereof and antidigoxin, etc. By having a ligand conjugated to the oligonucleotide, continues the patentee, one can sequester the eTag conjugated oligonucleotide probe and its target with the receptor, remove unhybridized eTag reporter conjugated oligonucleotide and then

release the bound eTag reporters or bind an oppositely charged receptor, so that the ligand-receptor complex with the eTag reporter migrates in the opposite direction. Figs. 3A and 3B support the fact that Singh does not teach anything more than using biotin or avidin or digoxin or anti-digoxin as a ligand or receptor linked to an oligonucleotide. Fig. 3B shows biotin linked to an e-Tag. There is no disclosure of digoxigenin linked biotin.

The Office Action continues by asserting that Oh teaches the use of digoxigenin linked biotin referring to Oh, col. 16, lines 30-38, in support thereof. Oh teaches tridentate conjugates involving small molecules, which are linked to an analyte as the second member of the tridentate. For example, for theophylline Oh mentions biotin-theophylline-DNP or biotin-theophylline-biotin. At the cited passage Oh also indicates that other analyte drugs that may be assayed include digoxin, etc. Accordingly, the skilled person would understand that, if the analyte is digoxin, then the tridentate would have two small molecules linked to digoxin such as, for example, biotin-digoxin-biotin. The tridentates are used in competition assays where the analyte member of the tridentate competes with the analyte of the sample for binding to a specific binding partner for the analyte (col. 15, lines 26-40).

Oh's disclosure has no relevance to the teaching of Singh and, thus, one skilled in the art would not be motivated to use the tridentate conjugate of Oh in the method of Singh. Furthermore, even if the skilled artisan were motivated to make the combination imagined in the Office Action, one still would not be in possession of the invention of Claims 3 and 37-43. There is no recognition of using digoxigenin linked biotin as a substrate in an assay where cleavage releases a detectable product. At most, the combined teaching of Singh and Oh would employ a tridentate conjugate as a capture ligand as taught by Singh.

Claims 44-46 were rejected under paragraph (a) of the above code section as being unpatentable over Singh in view of Oh. For reasons similar to those discussed above with regard to the rejection of Claims 3 and 37-43 under the above code section, Claims 44-46 are patentable over the combination of teachings of Singh and Oh. Again, Singh specifically teaches the use of capture ligands to separate components of his assay mixture and not as a substrate that is cleaved to produce a detectable product that is detected by binding to third specific binding pair member as in the present claims.

Conclusion

Applicant has demonstrated that Claims 1-6 and 37-46 satisfy the requirements of 35 U.S.C. 112, 102 and 103. Allowance of the above-identified patent application, it is submitted, is in order.

Respectfully submitted,

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